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A placebo controlled comparison of the effects of pirenzepine and amitriptyline on the tyramine pressor test in healthy volunteers

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The possibility of an interaction between pirenzepine, an antimuscarinic drug structurally similar to the tricyclic antidepressants, and sympathomimetic agents was investigated in a group of healthy volunteers. The effect of pirenzepine on response to intravenous tyramine was compared with that of placebo and amitriptyline. The mean dose of tyramine required to elevate systolic blood pressure by 30 mm Hg was 5.0 mg (± s.d. 0.8) after placebo, 5.1 mg (± 1.0) after pirenzepine and 11.3 mg (± 1.8) after amitriptyline. These results suggest that pirenzepine will not potentiate the effects of concurrently administered sympathomimetic drugs.

Keywords pirenzepine amitriptyline tyramine pressor test

Introduction

Pirenzepine is an anticholinergic drug of value in the treatment of peptic ulceration (Chierichetti *et al.*, 1979). It is relatively selective for gastric mucosal receptors as opposed to muscarinic receptors in other tissues (Hammer & Giachetti, 1984). The therapeutic advantage is that gastric and pepsinogen secretion is reduced with a lower incidence of unwanted effects, such as mydriasis, dry mouth and inhibition of 'gastric emptying' (Chierichetti *et al.*, 1979).

Although an antimuscarinic drug, the chemical structure of pirenzepine is related to the tricyclic antidepressants (Figure 1). The latter group of drugs inhibit the uptake of biogenic amines and potentiate the action of sympathomimetic agents and monoamine oxidase inhibitors (Baldessatini, 1980). There is then a theoretical possibility that pirenzepine might exhibit similar pharmacological interactions (Data Sheet Compendium, 1984–85). Experiments in cats have shown that intravenous pirenzepine potentiates the blood pressure responses to adrenaline and noradrenaline (unpublished data on Boots Company files). However, no data is available for humans.

The tyramine pressor test is a well documented technique for assessing the potential of a drug to act as a reuptake inhibitor (Ghose, 1980; Turner, 1980). It is reproducible and relatively safe from cardiac arrhythmias and the effects of tricyclic antidepressants on this test have been particularly well studied. We have compared the effects of pirenzepine, amitriptyline and placebo on the pressor response to tyramine in a group of healthy volunteers.

Methods

Nine volunteers (five female) aged 21 to 40 years were studied. They were all healthy, as judged by clinical examination, full blood count and biochemical profile. None had a history of psychiatric illness. They were non-smokers and were not taking any medication apart from that

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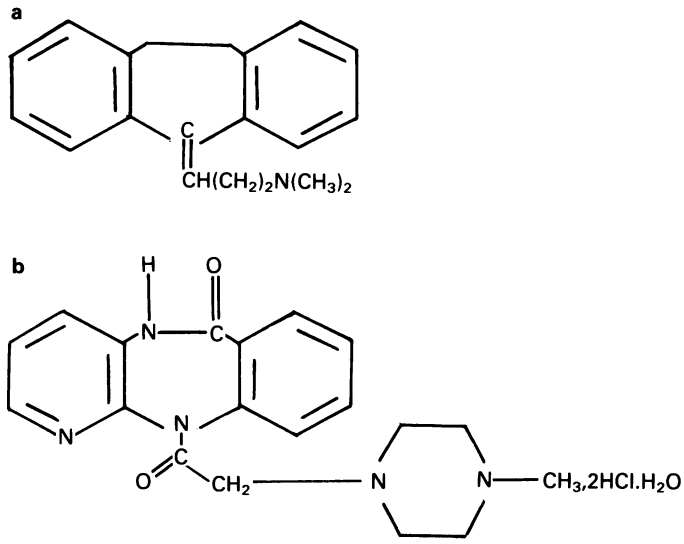

Figure 1 The chemical structure of **(a)** amitriptyline and **(b)** pirenzepine.

prescribed in the study. They were given a list of foods of high tyramine content which they were requested to avoid for 48 h prior to each tyramine pressor test. Each gave his/her written consent to participate in the study which was approved by the Birmingham Central Ethics Committee.

Each volunteer attended a hospital side room at 09.00 h on three occasions, not less than 1 week apart, for a tyramine pressor test. Each volunteer took three treatments, one prior to each visit. The three treatments were: pirenzepine, 50 mg 08.00 h and 20.00 h for 3 days and 08.00 h the morning of the pressor test; placebo pirenzepine, using the same dosing schedule as active pirenzepine; and amitriptyline, 50 mg 20.00 h the night before and 50 mg 08.00 h the morning of the test. The three treatments were randomised by an independent investigator; the pirenzepine was therefore given double-blind.

The tyramine pressor test was conducted according to Ghose *et al.* (1976) with certain modifications. Basal SBP for each visit was the mean of three readings after 30 min rest in the supine position. Tyramine (1.0 mg) was administered by rapid injection in 0.9% saline (total volume 5 ml) through an indwelling cannula in an antecubital vein. Systolic blood pressure (SBP) was recorded every 20–25 s by a Critikon Dinamap 1846 vital signs monitor until basal SBP was re-established. Further injections of tyramine were given at 5 min intervals. The dose was increased according to individual response until a rise in SBP of 30 mm Hg or greater was obtained.

Analysis

The dose of tyramine required to elevate SBP by 30 mm Hg, T30, was determined from the dose-response curve by interpolating between two points assuming a linear relationship.

Results

For each treatment, a dose-dependent increase in SBP was obtained with successive injections of tyramine. As expected, amitriptyline displaced the dose-response curve to the right.

The mean T30 (± s.d.) during treatment with placebo, pirenzepine and amitriptyline are given in Table 1. It is conventional to express the results as a ratio of T30 for the active drug to T30 for placebo and these dose-ratios are included in the table. The higher the ratio, the greater the decrease in sensitivity to tyramine and the greater the noradrenaline reuptake blocking effect of the drug.

Table 1 Comparison of the effects of placebo, pirenzepine and amitriptyline on response to intravenous tyramine

	Placebo	*Pirenzepine*	*Amitriptyline*
Mean T30 (± s.d.)	5.0 mg (± 0.8)	5.1 mg (± 1.0)	11.3 mg (± 1.8)
Dose-ratio		1.0	2.3

Overall amitriptyline reduced sensitivity to tyramine by a factor of 2.3. Interindividual response varied from 1.9 to 3.0. In contrast, pirenzepine had no significant effect on the pressor response; the mean T30 was 5.1 mg (± s.d. 1.0) and the dose ratio was 1.0, range 0.8 to 1.2. Neither active treatment significantly affected basal systolic blood pressure.

Discussion

The tyramine pressor test has become a standard test for assessing the effects of drugs, particularly new psychotropic drugs, on peripheral adrenergic activity (Ghose, 1980). Tyramine is an indirectly acting sympathomimetic amine which produces its pharmacological action by releasing noradrenaline from nerve terminals. Tyramine is taken up by nerve terminals by the same membrane pump as noradrenaline. Thus drugs which inhibit the uptake of this catecholamine also inhibit the uptake of tyramine and reduce the pressor response to an intravenous bolus of the amine (Ghose, 1980; Turner, 1980).

As expected, amitriptyline reduced sensitivity to the pressor effects of tyramine in all subjects. The mean reduction, by a factor of 2.3, is less than that reported by other authors (Ghose, 1980; Ghose *et al.*, 1976) who give mean dose-response ratios between 4 and 6. However, these authors acknowledged considerable inter-individual variation in the effect of amitriptyline. Furthermore, these investigators conducted their studies after 2 or more weeks treatment with the antidepressant, whilst in our study, the pressor test was performed after only two doses of the drug. The purpose of amitriptyline in this study was to act as a reference drug to demonstrate that our method can detect an alteration in sensitivity to tyramine and give a standard by which to compare the potency of pirenzepine in this respect.

We were unable to show an effect of therapeutic doses of pirenzepine on sensitivity to intravenous tyramine. This is not altogether surprising as the tricyclic antidepressants as a group vary in potency for inhibiting the pressor response to tyramine, amitriptyline being the most potent. Our findings are in contrast to the experiments in cats which demonstrated that pirenzepine potentiates the blood pressure response to catecholamines. However, the cat is not a good animal model for humans and it is difficult to extrapolate the dose-response relationship to man; thus a higher dose of pirenzepine might be required to demonstrate this effect in man.

In conclusion, we have found no evidence for an effect of pirenzepine in therapeutic doses on sensitivity to tyramine in a group of healthy volunteers. This study would suggest that pirenzepine is unlikely to potentiate the effects of concurrently administered sympathetic agents.

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